Electronically Filed On: 1-31-2007

PATENT
Attorney Docket No. 34170-701.501

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:	Confirmation No.: **4993**
Inventor: Peter S. Lu et al.	Examiner: Lucas, Zachariah
Application No.: 10/630,590	Group Art Unit: 1648
Filed: July 29, 2003	Customer No. **21971**
Title: **METHODS OF DIAGNOSING CERVICAL CANCER**	

DECLARATION UNDER 37 C.F.R. §1.131

I, Peter S. Lu, declare as follows:

1. I am a co-inventor of claims 1, 3-8, 10-22 and 24-26 of the patent application identified above and a co-inventor of the subject matters described and claimed therein.

2. Currently I am president and chief executive officer of Arbor Vita Corporation. In 1998 I founded Arbor Vita Corporation to discover the biological roles of PDZ proteins and apply them to the development of therapeutics and diagnostics. Previously, I directed the Stanford Psoriasis Treatment Center and was a Postdoctoral Fellow at the Howard Hughes Medical Institute at Stanford University. I completed my residency in Dermatology at Stanford University School of Medicine. I received a degree of B.S. in Biology from the California Institute of Technology, M.S. in Microbiology/Immunology from the University of Washington and M.D. from the University of Washington Medical School. The detail of my education and professional experiences is provided in the attached *curriculum vitae* of mine.

3. I, together with co-inventors Johannes Schweizer, Chamorro S. Diaz-Sarmiento, and Michael P. Belmares, conceived and reduced to practice in this country the invention claimed in claims 1, 3-8, 10-22 and 24-26 in the above-referenced application prior to September 6, 2001, the publication date of Thomas et al. (2001) *Oncogene* 22:5431-5439.

4. Prior to September 6, 2001 we conceived that the E6 protein of oncogenic human Papillomavius (HPV) has a C-terminal domain with a consensus sequence of –X-(S/T)-X-(V/I/L) that should be recognized and specifically bound to by a PDZ domain, such as domain 2 of MAGI-1, while non-oncogenic or low risk HPV E6 sequences should not. We developed assays to assess the binding interaction between the C-terminal domain of E6 protein of various oncogenic and non-oncogenic strains of HPV, such as the "G Assays" described in above-referenced application serial No. 10/630,590 at pages 43-46, and in provisional application No. 60/309,841 filed on August, 3, 2001 at pages 32-36.

5. Prior to September 6, 2001 we designed and purchased from commercial suppliers peptides (*see* **Exhibit A** for evidence of purchase with dates obscured) containing the consensus C-terminal sequences derived from various oncogenic strains of HPV, and C-terminal sequences from non-oncogenic strains of HPV. **Table 1** below lists the sequences of such peptides with the C-terminal consensus sequences of oncogenic strains of HPV highlighted in bold. As listed in **Table 1**, besides peptides which have the native sequences of the C-termini of the HPV strains, we also designed peptides that are derived from the native sequences of the C-termini by substituting amino acid residues (especially cysteine residues) outside the consensus 4 amino acid C-terminal sequences with other amino acid residues to avoid complications resulting from aberrant folding of the native peptides due to cross-linking of the cysteine residues that causes aggregation of the peptides. *See* designed peptide sequences labeled with "(modified)" or "(cysteine-free)" in **Table 1**.

Table 1. Sequences of C-terminal peptides derived from E6 protein of various HPV strains.

AVC Name	Sequence	oncogenic
HPV E6 16	WTGRCMSCCRSSRTRR**ETQL**	Y
HPV E6 16 (Modified)	TGRGMSGGRSSRTRR**ETQL**	Y
HPV E6 18	HSCCNRARQERLQRRR**ETQV**	Y
HPV E6 18 (Modified)	SGGNRARQERLQRRR**ETQV**	Y
HPV-E6 31	GRWTGRCIACWRRPRT**ETQV**	Y
HPV E6 33	CAACWRSARRRRLQRRR**ETAL**	Y
HPV E6 33 (modified)	AAGGRSARGGRLQGRR**ETAL**	Y
HPV E6 35	GRWTGRCMSCWKPTRR**ETEV**	Y
HPV E6 35 (cysteine-free)	GRWTGRAMSAWKPTRR**ETEV**	Y
HPV E6 36 (cysteine-free)	RVRNAWKGIARQAKHFYNDW	N
HPV-E6 51	CANCWQRTRQRRLQRRN**ETQV**	Y
HPV E6 52	MGRWTGRCSECWRPRP**VTQV**	Y
HPV E6 52 (modified)	SEGGRPTRGPRLQGRR**VTQV**	Y
HPV E6 57	HCMNCAPRCMENAPALRTSH	N
HPV E6 57 (cysteine-free)	HAMNAAPRAMENAPALRTSH	N
HPV E6 58	GRWTGRCAVCWRPRRR**QTQV**	Y
HPV E6 58 (modified)	AVGGRPARGGRLQGRR**QTQV**	Y
HPV E6 63	VHKVRNKFKAKCSLCRLYII	N
HPV-E6 66	TGSCLQCWRHTSRQAT**ESTV**	Y
HPV E6 66 (cysteine-free)	TGSALQAWRHTSRQAT**ESTV**	Y
HPV-E6 70	RHCWTSNREDRRRIRR**ETQV**	Y
HPV-E6 77	GHWRGSCLHCWSRCMGQSRQ	N
HPV E6 77 (modified)	GGGRGSGLAGGSRGGGQSRQ	N
HPV-E6 80	QFHKVRRNWKGLCRHCGSIE	N

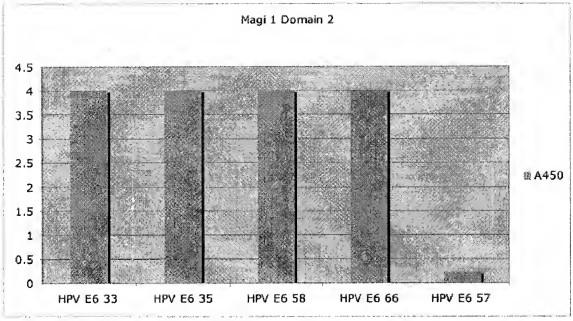
6. Prior to September 6, 2001 we used the G Assays to assess the interactions of peptides (**Table 2**) derived from the C-terminal 19-20 amino acids of E6 proteins from oncogenic HPV types 33, 35, 58, 66 and non-oncogenic type 57. Peptide concentrations used in the G-assay were 10 uM, 1 uM, 10 uM, 3 uM, and 10 uM, respectively. **Figure 1** summarizes the results of these experiments with the C-terminal consensus sequences of oncogenic strains of HPV highlighted. The absorbance value at 450 nm indicates the amount of HPV peptides bound to MAGI-1 domain 2. **Exhibit B** is a copy of pages from lab notebooks recording such experiments on which the dates have obscured.

7. As shown in **Figure 1**, prior to September 6, 2001 we demonstrated that all four of peptides derived from the E6 protein of oncogenic HPV strains 33, 35, 58 and 66 bound MAGI-1 PDZ domain 2 strongly at 1-10 uM peptide concentrations. In contrast, the E6 sequence from non-oncogenic HPV type 57 did not bind to MAGI-1 domain 2. In addition, peptides derived from the E6 protein of oncogenic HPV strains 16 and 18 that share the same consensus C-terminal sequence as strains 33, 35, 58 and 66 were later demonstrated to bind to MAGI-1 domain 2. Thus, since the claimed invention is a method or system for detecting the presence of an oncogenic HPV in a sample by using a PDZ domain polypeptide of less than 1000 amino acids in length and comprising the amino acid sequence of MAGI-1 PDZ domain 2, the claimed invention was conceived and reduced to practice prior to September 6, 2001.

Table 2. Sequences of C-terminal peptides derived from E6 protein of various HPV strains.

HPV Type	E6 C-terminal sequence	Derived from Oncogenic HPV E6
HPV 33 (modified)	AAGGRSARGGRLQGRR**ETAL**	Y
HPV 35 (cysteine-free)	GRWTGRAMSAWKPTRR**ETEV**	Y
HPV 58 (cysteine-free)	AVGGRPARGGRLQGRR**QTQV**	Y
HPV 66 (cysteine-free)	TGSALQAWRHTSRQAT**ESTV**	Y
HPV 57 (cysteine-free)	HAMNAAPRAMENAPALRTSH	N

FIGURE 1: Binding strength of HPV E6 peptides with PDZ domain 2 of MAGI-1



8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By: _____

Peter S. Lu, M.D.

Date: Jan 31, 2007 Country of Citizenship: U.S.A.